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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,774	SYLVAN, ANNA	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-15, 17, 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-15, 17, 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed January 26, 2004. Currently, claims 1, 3-15, 17, 19-23 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and applicant's arguments.

4. The rejection of Claims 1-6, 8, 17-22 under 35 U.S.C. 102(a) by Bellman et al. (Poster presented April 2000 at Human Genome Project Meeting) has been withdrawn in view of the declaration by Anna Sylvan stating the subject matter of the poster was derived from her work.

Specification

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a **separate sheet** within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The response has provided a new abstract, however the abstract is not on a separate sheet. Thus, the abstract is objected to.

New Grounds of Rejection/Objection Necessitated by Amendment

Claim Objections

6. Claims 3-6, 19-23 are objected to because they depend from Claims 2 and 16 which have been cancelled. Therefore, the claims are not proper. Appropriate correction is required.

7. Claim 9 is objected to because they depend from Claims 8 and 1. Claim 1 has been amended to require primer extension reaction. Claim 9 does not appear to further limit Claim 8 as this limitation is already present in Claim 8.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 17, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Lapidus et al. (US Pat. 6,020,137, February 1, 2000).

Lapidus et al. (herein referred to as Lapidus) teaches a method for detecting of loss of herterozygosity in a pooled patient population. Lapidus teaches that a sample may be derived from pooled specimens from a plurality of members of a population (col.

2, lines 49-53). Lapidus teaches a method comprising pooling samples, hybridizing probes to the sample which are immediately adjacent to a single-based polymorphism, exposing the pooled sample to a plurality of different dideoxy nucleotides; washing the sample, determining which of the dideoxy nucleotides are incorporated into the probes and detecting the incorporated dideoxy nucleotide at the site (see Claim 38, for example of Lapidus)(limitations of Claim 1). Lapidus teaches using allelic DNA adjacent to the polymorphic nucleotide as a template, hybridized probe is extended by the addition of a single dideoxynucleotide that is the binding partner for the polymorphic nucleotide (col. 5, lines 50-55). Dideoxynucleotides which have been incorporated into the probe extensions are detected by determining the number of bound extended probes bearing each of the two dideoxy nucleotides. Lapidus teaches that a scintillation counter may be used (limitations of Claim 3). Lapdius teaches two chain terminating nucleotides are labeled with different isotopes. The primer extension products may be gel electrophoresed and exposed to an imager to detect both isotopes (col. 13, lines 45-50)(limitations of Claim 7). Therefore, since Lapidus teaches every limitation of the instant claims, Lapidus anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 4-7, 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren-2 (WO 98/28440, published July 2, 1998) or in view of Lapidus et al. (US Pat. 6,020,137, February 1, 2000).

This rejection would be appropriate in the event that Claim 3 depended from Claim 1 and Claim 19 depended from Claim 17.

Nyren-2 teaches a method of sequencing DNA based on the detection of the release of pyrophosphate. In example 2, Nryren-2 teaches pyrosequencing on a PCR product. The biotinylated PCR products were immobilized onto a Dynabead (page 38)(limitations of Claim 7, 23). The primer was hybridized to the template and incubated with polymerase (page 38). The sequence procedure was carried out as a stepwise elongation of the primer-strand upon sequential addition of the different deoxynueoside tripohsphates and simultaneous degradation of the nucleotides by apyrase (col. 38)(limitations of Claim 6, 22). Released Ppi due to nucleotide incorporated was detected (page 39)(limitations of Claim 4, 20). Thus, the base was identified at a target position. Nyren-2 teaches identifying a base at a target position in a sample DNA sequence wherein an extension primer, which hybridizes to the sample DNA immediately adjacent to the target position is provided and the sample DNA and extension primer are subjected to polymerase reaction in the presence of a deoxynucleotide where the deoxynucleotide will only become incorporated and release pyrophosphate (PPI) if it is complementary to the base in the target position. Any release of Ppi being detectable enzymically. Nyren-2 teaches including a nucleotide degrading enzyme during the polymerase reaction step, such that unincorporated

nucleotides are degraded (page 3, para 2). Nyren-2 specifically teaches that apyrase is a nucleotide-degrading enzyme (page 4). Nyren-2 teaches that including a nucleotide-degrading enzyme allows the sequencing procedure to proceed without washing the template between successive nucleotide additions. Additionally, since washing steps are avoided, it is not necessary to add new enzymes (page 5).

Nyren does not specifically teach pooling the nucleic acid molecules into a sample and determining the frequency of an allele in a population.

However, Lapidus et al. (herein referred to as Lapidus) teaches a method for detecting of loss of herterozygosity in a pooled patient population. Lapidus teaches that a sample may be derived from pooled specimens from a plurality of members of a population (col. 2, lines 49-53). Pooled samples are useful to screen large numbers of individuals, to identify genomic features such as mutations or SNPs indicative or associated with a disease (col. 4, lines 35-40). Lapidus teaches a method comprising pooling samples, hybridizing probes to the sample which are immediately adjacent to a single-based polymorphism, exposing the pooled sample to a plurality of different dideoxy nucleotides; washing the sample, determining which of the dideoxy nucleotides are incorporated into the probes and detecting the incorporated dideoxy nucleotide at the site (see Claim 38, for example of Lapidus)(limitations of Claim 1). Lapidus teaches using allelic DNA adjacent to the polymorphic nucleotide as a template, hybridized probe is extended by the addition of a single dideoxynucleotide that is the binding partner for the polymorphic nucleotide (col. 5, lines 50-55). Dideoxynucleotides which have been incorporated into the probe extensions are detected by determining the

number of bound extended probes bearing each of the two dideoxy nucleotides. Lapidus teaches that a scintillation counter may be used (limitations of Claim 3). Lapdius teaches two chain terminating nucleotides are labeled with different isotopes. The primer extension products may be gel electrophoresed and exposed to an imager to detect both isotopes (col. 13, lines 45-50)(limitations of Claim 7).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Nyren-2 which detect alleles by the primer extension method which detect the release of pyrophoshate with the pooling primer extension method of Lapidus. The ordinary artisan would have been motivated to have pooled a population for the expected benefits taught by Lapidus. Lapidus specifically teaches that pooled samples are useful to screen large numbers of individuals, to identify genomic features such as mutations or SNPs indicative or associated with a disease (col. 4, lines 35-40). Therefore, applying the primer extension method which detects Ppi released with the pooling primer extension method of Lapidus would have been obvious to also for more rapid high throughput analysis of samples.

10. Claims 8-11, 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. (US Pat. 6,020,137, February 1, 2000) in view of Breen et al. (BioTechniques, Vol. 28, No. 3, pages 464-470, March 2000).

Lapidus et al. (herein referred to as Lapidus) teaches a method for detecting of loss of herterozygosity in a pooled patient population. Lapidus teaches that a sample may be derived from pooled specimens from a plurality of members of a population (col.

2, lines 49-53). Pooled samples are useful to screen large numbers of individuals, to identify genomic features such as mutations or SNPs indicative or associated with a disease (col. 4, lines 35-40). Lapidus teaches a method comprising pooling samples, hybridizing probes to the sample which are immediately adjacent to a single-based polymorphism, exposing the pooled sample to a plurality of different dideoxy nucleotides; washing the sample, determining which of the dideoxy nucleotides are incorporated into the probes and detecting the incorporated dideoxy nucleotide at the site (see Claim 38, for example of Lapidus)(limitations of Claim 1). Lapidus teaches using allelic DNA adjacent to the polymorphic nucleotide as a template, hybridized probe is extended by the addition of a single dideoxynucleotide that is the binding partner for the polymorphic nucleotide (col. 5, lines 50-55). Dideoxynucleotides which have been incorporated into the probe extensions are detected by determining the number of bound extended probes bearing each of the two dideoxy nucleotides. Lapidus teaches that a scintillation counter may be used (limitations of Claim 3). Lapdius teaches two chain terminating nucleotides are labeled with different isotopes. The primer extension products may be gel electrophoresed and exposed to an imager to detect both isotopes (col. 13, lines 45-50)(limitations of Claim 7).

Lapidus does not specifically teach determining the amount or concentration of nucleic acids in each sample prior to pooling.

However, Breen et al. (herein referred to as Breen) teaches methods of pool construction and methods of testing the sensitivity of the DNA pooling method. Breen teaches concentrations of samples may be estimated by fluorimetry. Moreover, Breen

teaches testing the accuracy of the pooling protocol by comparing the frequencies derived from individual genotyping with tests using spiking where additional alleles were introduced into DNA pools (page 464, col. 3). Breen teaches dividing the pools into aliquots and the amount of DNA from a homozygote that was equivalent to one, two, five and ten alleles was added to the aliquots. PCR (primer-extension reaction) was carried out on the pools. Moreover, additional calibration pools were constructed and DNA from different homozygotes was mixed together in different ratios (0:100, 20:80, 40:60, etc)(page 464, col. 3). Breen teaches analyzing SNP in the DRD2 gene and the COLIA1 gene (page 464, col. 3). Figure 2 illustrates a calibration curve to correct for the distorted allele frequencies derived from pooling (page 466). Breen teaches that the results of the Taqman assay to determine genotypes was highly consistent and reproducible (page 469, col. 2). The Taqman assay uses both primers and probes (primer extension reaction). Breen teaches using allele specific fluorescent probes to determining the number of copies of the two alleles. Breen illustrates the difference between the estimate and the results of the differing levels of probes was significant, with a p value equivalent to $P<0.0001$ (page 469, col. 3). Thus, Breen teaches that copies of the two alleles may be determined using fluorescent probes, i.e. the total of the two alleles provides an accurate indication of the concentration of the original sample. While Breen specifically teaches using the same concentration of each DNA sample, Breen does not specifically teach determining the concentration of the nucleic acid by a primer extension reaction prior to pooling.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Lapidus with the specific teachings of Breen that concentrations of samples should be ensured. It would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Lapidus to ensure that the problems enumerated by Breen were considered. The ordinary artisan would have been motivated to have detected concentrations of each DNA sample using a fluorimeter with a method using allele-specific fluorescent probes as taught by Breen. Breen teaches "it seems the only limiting factor on accuracy in this system is the variation introduced when the pools are constructed and the DNA concentration measurements made." (page 470, col. 1). To obtain accurate information regarding the true frequencies of a pooled population, it is essential that each member of the population is represented in equal concentrations within the sample. For example if the population is comprised of two homozygote individuals, aa and AA, and the pool is designed to contain 10 µg of DNA from the individual with "aa" and 90 µg of DNA from the individual with "AA", the estimated frequency of the alleles would be 0.1 for "a" and 0.9 for "A". This would not accurately reflect the true population frequency. In contrast, a pool designed to contain 50 µg of DNA from the individual with "aa" and 50 µg of DNA from the individual with "AA", the estimated frequency of the alleles would be 0.5 for "a" and 0.5 for "A", a true estimate of the frequencies of the two alleles in the population. Therefore, in order to obtain a true estimate of the frequency of alleles in a population, adjusting the amount or concentration of a nucleic acid in a sample is essential. It would have been obvious to

the ordinary artisan to dilute or increase nucleic acid concentrations to ensure equal concentrations within each of the samples prior to pooling. Thus, because Breen illustrates the accuracy of the allele-specific fluorescent probe system in determining the copy numbers of various alleles in a particular sample, the concentration (the total of all possible alleles in the sample) may be accurately determined. Since the ordinary artisan performing the method of Breen for determining the allele frequencies in a pooled DNA sample using a 5' fluorescently labeled primer teaches the necessity of having equal concentrations of each sample, the ordinary artisan would recognize that a method of determining concentrations of samples using a Taqman assay would be an alternative means of obtaining information regarding concentration of a sample. Breen teaches that the results of the Taqman assay to determine genotypes was highly consistent and reproducible (page 469, col. 2).

With respect to Claim 14-15, Breen teaches DNA from different homozygotes was mixed together in different ratios (as seen in Figure 2). Figure 2 illustrates pooling of samples at different concentrations to determine the relative concentration in each reference sample, thereby generating a calibration cure to correct for the distorted allele frequencies derived from pooling analysis.

Therefore, using the Taqman assay would be an equivalent means of determining the concentration of a particular sample and the ordinary artisan would have been motivated to have used the assay for the benefit of using a highly consistent and reproducible assay for determining the concentration of nucleic acids present in a sample.

11. Claims 8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. (US Pat. 6,020,137, February 1, 2000) in view of Germer et al. (Genome Research, Vol. 10, No. 2, pages 258-266, February 23, 2000).

Lapidus et al. (herein referred to as Lapidus) teaches a method for detecting of loss of herterozygosity in a pooled patient population. Lapidus teaches that a sample may be derived from pooled specimens from a plurality of members of a population (col. 2, lines 49-53). Pooled samples are useful to screen large numbers of individuals, to identify genomic features such as mutations or SNPs indicative or associated with a disease (col. 4, lines 35-40). Lapidus teaches a method comprising pooling samples, hybridizing probes to the sample which are immediately adjacent to a single-based polymorphism, exposing the pooled sample to a plurality of different dideoxy nucleotides; washing the sample, determining which of the dideoxy nucleotides are incorporated into the probes and detecting the incorporated dideoxy nucleotide at the site (see Claim 38, for example of Lapidus)(limitations of Claim 1). Lapidus teaches using allelic DNA adjacent to the polymorphic nucleotide as a template, hybridized probe is extended by the addition of a single dideoxynucleotide that is the binding partner for the polymorphic nucleotide (col. 5, lines 50-55). Dideoxynucleotides which have been incorporated into the probe extensions are detected by determining the number of bound extended probes bearing each of the two dideoxy nucleotides. Lapidus teaches that a scintillation counter may be used (limitations of Claim 3). Lapdius teaches two chain terminating nucleotides are labeled with different isotopes.

The primer extension products may be gel electrophoresed and exposed to an imager to detect both isotopes (col. 13, lines 45-50)(limitations of Claim 7).

Lapidus does not specifically teach determining the amount or concentration of nucleic acids in each sample prior to pooling.

Germer et al. (herein referred to as Germer) teaches a method for determining the allele frequency of biallelic polymorphisms in pooled samples. Specifically, Germer teaches a mixture of DNAs pooled from individual sample were subjected to primer pairs (e.g. a primer pair specific to one or the other SNP allelic variant), and detecting the frequency (page 259, col. 1). Germer teaches enhancing specificity of the kinetic PCR reaction by using Stoffel fragment Taq DNA polymerase (page 259, col. 1)(limitations of Claim 3). Germer teaches the amplification efficiencies for the two allele-specific PCRs may differ slightly but this can be measured and compensated for by performing the assay on a DNA known to be heterozygous for the SNP of interest. Germer teaches that the deltaC for this DNA should equal zero if the PCRs are equally efficient (page 259, col. 2). Germer teaches that any deviation can then be subtracted from all deltaC measurements to compensate for differential amplification efficiencies (page 259, col. 2). Germer teaches that error introduced by unequal amplification efficiency of the two allele-specific primers for each polymorphism may be corrected for (page 261, col. 1). Germer teaches method for avoiding the formation and potential interference of template independent generation of primer artifact by using UNG and heat-activated polymerase enzyme. Moreover, using Stoffel fragment of Taq polymerase minimizes the problem because it is highly discriminatory and not very

processive (page 260, col. 2). The relative amounts of each allele in a sample are quantified (abstract). As seen in Table 2, the allele frequency measurements on a pool of 100 human DNAs in three genes illustrate very highly correlated results. Germer teaches "in conducting association studies using pools of DNA, accurate quantitation of the individual DNAs is important lest artifactual allele discrepancies between pools arise (page 263, col. 2). Germer teaches that the "simplest safeguard against errors arising from the pooling process would be to validate the pools by doing genotyping of the individual sample and showing concordance between allele counting and frequency measurement on the pool. Germer teaches that Tm-shift genotyping is a good choice because it uses the same allele-specific PCR conditions and two of the same three primers as the described method (page 263, col. 2). The methods section teaches that the samples were constructed by mixing two homozygous human DNA samples in various proportions by combining known amounts of homozygous DNA samples (limitations of Claim 8). Germer teaches his method of determining SNP allele frequencies in pooled sample has a number of advantages (1) it is not based on expensive fluorescently labeled primers or probes (2) it is a homogenous assay that requires no post-PCR processing (3) it operates under uniform conditions without the need for marker specific assay optimization (4) it is accurate and (5) it promises to be inexpensive, time-saving and precise to allow detection of relatively weak genetic associations (Page 258-259).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Lapidus with the specific

teachings of Germer that concentrations of samples should be ensured. Germer specifically teaches using the same concentration of each DNA sample is important lest artifactual allele discrepancies between pools arise, however, Germer does not specifically adjusting the amount of nucleic acids to contain substantially the same amount.

However, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Germer which detects concentrations of each DNA sample using a Tm-shift genotyping assay to detect quantities with a further method step of adjusting the concentration. Since Germer teaches "in conducting association studies using pools of DNA, accurate quantitation of the individual DNAs is important lest artifactual allele discrepancies between pools arise (page 263, col. 2) and the "simplest safeguard against errors arising from the pooling process would be to validate the pools by doing genotyping of the individual sample and showing concordance between allele counting and frequency measurement on the pool", it would have been obvious to adjust the amount or concentration of the nucleic acids present in the event that a discrepancy was ascertained. To obtain accurate information regarding the true frequencies of a pooled population, it is essential that each member of the population is represented in equal concentrations within the sample. For example if the population is comprised of two homozygote individuals, aa and AA, and the pool is designed to contain 10 µg of DNA from the individual with "aa" and 90 µg of DNA from the individual with "AA", the estimated frequency of the alleles would be 0.1 for "a" and 0.9 for "A". This would not accurately reflect the true population

frequency. In contrast, a pool designed to contain 50 µg of DNA from the individual with "aa" and 50 µg of DNA from the individual with "AA", the estimated frequency of the alleles would be 0.5 for "a" and 0.5 for "A", a true estimate of the frequencies of the two alleles in the population. Therefore, in order to obtain a true estimate of the frequency of alleles in a population, adjusting the amount or concentration of a nucleic acid in a sample is essential. It would have been obvious to the ordinary artisan to dilute or increase nucleic acid concentrations to ensure equal concentrations within each of the samples prior to pooling.

With respect to Claim 11, Germer teaches assaying for three SNPs in the samples. Therefore, any one of these polymorphisms may be considered a reference polymorphism.

With respect to Claim 12, Germer teaches methods of ensuring that the error introduced by unequal amplification efficiency of the two primers for each polymorphism is corrected. Germer teaches correcting for the error between unequal amplification efficiency. Therefore, it would have been obvious to the ordinary artisan to correct for the polymorphism with respect to background signals and unequal amplification efficiencies.

With respect to Claim 13, the polymorphisms in the PON, B71 and CSTS genes are not located within a homopoymeric sequence, as exemplified by the sequence of the primers provided. Therefore, Germer teaches using a polymorphism not present in a homopolymeric sequence.

With respect to Claim 14-15, Germer teaches DNA from different homozygotes was mixed together in different ratios and analyzed (page 264, col. 2). Table 1 illustrates pooling of samples at different concentrations to determine the relative concentration in each reference sample, thereby generating a calibration cure to correct for the distorted allele frequencies derived from pooling analysis.

Conclusion

12. No claims allowable over the art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
March 25, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER